PATENT SPECIFICATION

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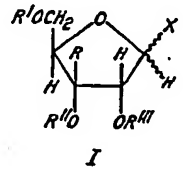
COMPLETE SPECIFICATION

D-Ribofuranose Derivatives

We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, New Jersey, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention concerns 3-alkyl ribofuranose compounds and esters thereof and methods for their preparation. Halo-substituted ribo-sugars and esters thereof in accordance with the present invention are useful as intermediates in the preparation of valuable substituted nucleosides. Some of these nucleosides are claimed in our copending application No. 49924/66 (Serial No. 1,163,103).

The compounds in accordance with the present invention have the formula:—



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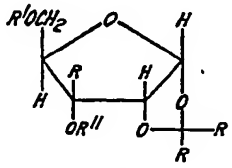


III

where each R is a C_{1-4} alkyl radical and may be the same as or different from any other radical denoted by R, X is a halogen atom or a hydroxy, C_{1-4} alkoxy, alkanoyloxy, aroyloxy, alkoxyaroyloxy, haloaroyloxy or nitrobenzoyloxy, e.g. acetoxy, propionoxy or butyroxy, and each of R′, R″ and R‴ is a hydrogen atom or an alkanoyl, aroyl, alkoxyaroyl, haloaroyl or nitrobenzoyl radical, provided that, in Formula I, when X is an alkanoyloxy, aroyloxy, alkoxyaroyloxy, haloaroyloxy or nitrobenzoyloxy radical, R′, R″ and R‴ are not hydrogen atoms.

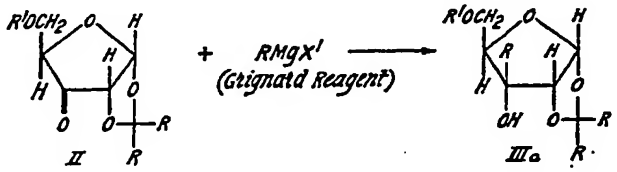
Typical of the R groups are methyl, ethyl and propyl radicals. Examples of X are chlorine and bromine atoms and hydroxy, acetoxy, propionoxy, and butyroxy radicals. Examples of R′, R″, and R‴ are hydrogen atoms and acetyl, propionyl, butyroyl, benzoyl, toluyl, xyloyl, methoxybenzoyl, ethoxybenzoyl, chlorobenzoyl, bromobenzoyl and nitrobenzoyl radicals.

In accordance with the present invention, the compounds of the invention are prepared by first treating a 5-O-R′-1,2-O-C_{3-9} alkylidene-D-*erythro*-3-pentulofuranose where R′ is as defined above with a Grignard reagent of the formula RM_gX' where R is as defined above and X′ is a halogen atom, to produce a 5-O-R′-1,2-C_{3-9} alkylidene-3-R-α-D-ribofuranose. This compound may then be treated by either of two methods. In the first method, the 5-O-R′-1,2-O-C_{3-9} alkylidene-3-R-α-D-ribo-

furanose intermediate is subjected to acidic alcoholysis using an alcohol of formula ROH to produce a C_{1-4} alkyl 5-O-R′-3-R-D-ribofuranoside which is acylated to produce a C_{1-4} alkyl 2,3,5-tri-O-R_4-3-R-D-ribofuranoside where R is as defined above and each of R_4 is an alkanoyl, aroyl, alkoxyaroyl, haloaroyl or nitrobenzoyl radical. This ribofuranoside may then be converted to the corresponding free sugar by basic solvolysis followed by a further hydrolysis by strong acid in an aqueous medium or it may be converted to a halo ester by a halogen replacement reaction in an appropriate solvent. In the second method, the 5-O-R′-1,2-O-alkylidene-3-R-α-D-ribofuranose intermediate is acylated under basic conditions to form the corresponding 3,5-di-O-R_4-1,2-,O-C_{3-5} alkylidene-3-R-D-ribofuranose intermediate which is hydrolysed in a strong acid and further acylated in an appropriate solvent to give the compounds of the present invention in which X, R′, R″, and R‴ are alkanoyl, aroyl, alkoxyaroyl, haloaroyl or nitrobenzoyl radicals.

The methods of preparing the compounds of the present invention are shown in the following reaction scheme:

STEP A

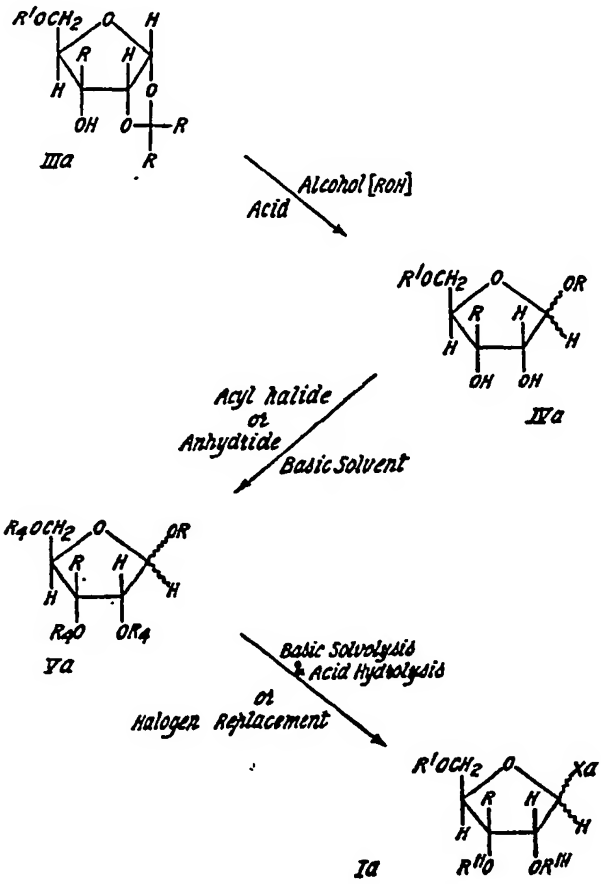


II IIIa

where R, R′, and X′ are as defined above. Intermediate compounds IIIa, which are also novel compounds, may be further reacted in STEP B by either of two methods to obtain the compounds I. Compounds IVa, IVb and Va are also novel and form part of this invention.

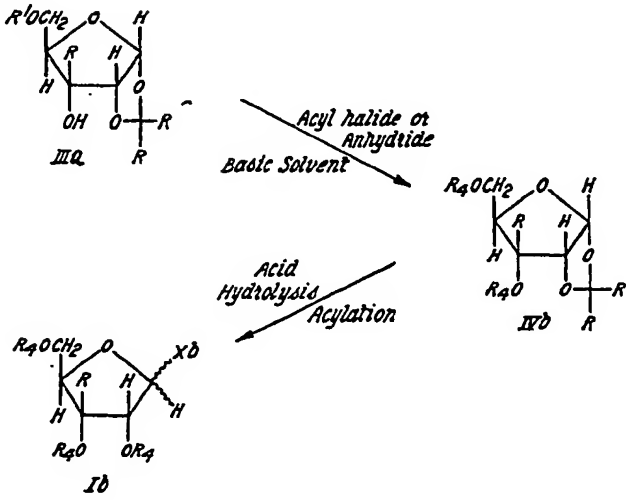
STEP B

Method B_a



where R, R_1, R′, R″, R‴ are as defined above and X_a is a halogen atom or hydroxyl radical.

Method B_b



where R, R_3, and R′ are as defined above and X_b is an alkanoyloxy, aroyloxy, alkoxyaroyloxy, haloaroyloxy or nitrobenzoyloxy radical.

Preferably, the 5-O-R′-1,2-O-C_{2-3} alkylidene-D-*erythro*-3-pentulofuranose is reacted with the Grignard reagent in essentially stoichiometric proportions at a temperature of from 5°C. to 80°C. for a period of from a few minutes to five hours. The Grignard reagents used in this reaction are C_1—C_4 alkyl magnesium halides. Examples of Grignard reagents are methyl magnesiumbromide, ethyl magnesiumbromide, methyl magnesium chloride, ethyl magnesiumchloride, methyl magnesiumiodide, ethtyl magnesiumiodide, and propyl magnesiumbromide.

In one aspect of the invention, Method B_a is then followed and compounds Ia, in which X is hydroxy or halogen, are obtained. In this method, the 5-O-R′-1,2-O-C_{3-9} alkylidene-3-R-α-D-ribofuranose is subjected to an acidic alcoholysis preferably by reaction with a strong acid such as hydrochloric acid, hydrobromic acid, ar sulfuric acid and a C_1—C_4 alcohol at a temperature of from 5°C. to 60°C. for a period of from a few minutes to 5 hours to produce a C_{1-4} alkyl 5-O-R′-3-R-D-ribofuranoside which is acylated under basic conditions with an acylating agent such as an acyl halide or an anhydride. Examples of acylating agents are benzoyl chloride, benzoyl bromide, nitrobenzoyl chloride, acetic anhydride and propionic anhydride. This acylation step is preferably carried out at a temperature of from 20°C. to 100°C. for a period of from two to 72 hours. The ribofuranoside thus produced may then be converted to the corresponding free sugar by a basic solvolysis, preferably by treatment with a C_{1-4} alcohol at a temperature of from 15°C. to 60°C. for a period of from a few minutes to a few hours and a further hydrolysis with a strong acid such as hydrochloric acid, hydrobromic acid or sulfuric acid in an aqueous medium. This acid hydrolysis step is preferably carried out at a temperature of from 5°C. to 50°C. for 2 hours to 24 hours. Alternatively, the ribofuranoside may be converted to the corresponding halo sugar by a halogen replacement reaction using the desired hydrogen halide in an appropriate solvent such as acetic acid, methylene chloride, tetrachloroethane, or propionic acid. This replacement reaction preferably takes place at a temperature of from 0°C. to 30°C. for a period of from a few minutes to a few days.

In another aspect of the invention, Method B_b is followed and compounds Ib, in which Xb is an acyl group, are obtained. In this method, the 5-O-R′-1,2-O-C_{3-9} alkylidene-3-R-α-D-ribofuranose is acylated under basic conditions preferably at a temperature of from 20°C. to 100°C. for a period of from 2 to 72 hours to form a 3,5-di-O-R_3-1,2-O-C_{3-9} alkylidene-3-R-α-D-ribofuranose. The acylating agent may be an acyl halide or an anhydride such as benzoyl chloride, benzoyl bromide, nitrobenzoyl chloride, acetic anhydride, or propionic anhydride. The basic conditions are preferably provided by a base such as pyridine, dimethylaniline, N-methylmorpholine or sodium acetate in an inert solvent such as benzene, dioxane, or tetrahydrofuran. The 3,5-di-O-R_3-1,2-O-C_{3-9} alkylidene-3-R-α-D-ribofuranose is then hydrolysed in a strong acid such as hydrochloric acid, hydrobromic acid, or sulfuric acid and further acylated with an anhydride such as acetic anhydride, propionic anhydride, or butyric anhydride in the corresponding acid as a solvent to form the compounds Ib of the present invention. This hydrolysis-acylation reaction is preferably carried out at a temperature of from 5°C. to 50°C. for a period of from 2 hours to 20 hours. All the reactions are preferably carried out in essentially stoichiometric proportions. Representative of the compounds of the present invention are 2-O-acetyl-3,5-di-O-benzoyl-3-methyl-D-ribofuranosyl chloride, 2-O-acetyl-3,5-di-O-benzoyl-3-methyl-D-ribofuranosyl bromide, 2-O-acetyl-3,5-di-O-benzoyl-3-ethyl-D-ribofuranosyl chloride, 2-O-acetyl-3,5-di-O-benzoyl-3-ethyl-D-ribofuranosyl bromide, 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl chloride, 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuronsyl bromide, 2,3,5-tri-O-benzoyl-3-ethyl-D-ribofuronsyl chloride, 2,3,5-tri-O-benzoyl-3-ethyl-D-ribofuranosyl bromide, 2,3,5-tri-O-benzoyl-3-propyl-D-ribofuranosyl chloride, 2,3,5-tri-O-benzoyl-3-propyl-D-ribofuranosyl bromide, 2,3-di-O-acetyl-5-O-benzoyl-3-methyl-D-ribofuranosyl chloride, 2,3-di-O-acetyl-5-O-benzoyl-3-methyl-D-ribofuranosyl bromide, 2,3-di-O-acetyl-5-O-benzoyl-3-ethyl-D-ribofuranosyl chloride, 2,3-di-O-acetyl-5-O-benzoyl-3-ethyl-D-ribofuranosyl bromide, 3-methyl-D-ribofuranose, 3-ethyl-D-ribofuranose, 3-propyl-D-ribofuranose, 1,2-di-O-acetyl-3,5-di-O-benzoyl-3-methyl-D-ribofuranose, 1,2-di-O-acetyl-3,5-di-O-benzoyl-3-ethyl-D-ribofuranose, 1,2-di-O-propionyl-3,5-di-O-benzoyl-3-methyl-D-ribofuranose, 1,2-di-O-propionyl-3,5-di-O-benzoyl-3-ethyl-D-ribofuranose, 1,2-di-O-butyryl-3,5-di-O-benzoyl-3-methyl-D-ribofuranose, 1,2-di-O-butyryl-3,5-di-O-benzoyl-3-ethyl-D-ribofuranose.

The following Examples illustrate the invention.

EXAMPLE 1

Preparation of 1,2-O-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose

A Grignard reagent, methyl magnesiumiodide, prepared from 690 mg. (28.4 mmoles) of magnesium and 3.85 grams (27.5 mmoles) of methyl iodide in 32 ml. of dry ether is added to a stirred solution of 1.0 gram (3.43 mmoles) of 1,2-O-isopropylidine-5-O-benzoyl-α-D-*erythro*-3-pentulofuranose in 100 ml. of dry ether at 5°C. After about 3 hours the reaction mixture is poured into a mixture of 50 grams of ammonium chloride, 200 ml. of ice and water, and 200 ml. of ether. The layers are separated and the aqueous phase is extracted with two 150-ml. portions of ether. The dried ($MgSO_4$) ether solution is concentrated to dryness and the residue (1.24 grams) is crystallized from ether. A total of 524 mg. of 1,2-O-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose, is obtained.

EXAMPLE 2.

A solution of 1.0 gram (3.25 mmoles) of 1,2-O-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose, obtained by the procedure of Example 1, in 25 ml. of 3% methanolic hydrogen chloride is kept at 25°C. for 75 minutes. The hydrogen chloride is neutralized by the portionwise addition of 2.5 grams (30 mmoles) of sodium bicarbonate. The mixture is filtered and the solid is washed with methanol. The filtrate plus washings are concentrated and the residue is leached with three 50-ml. portions of methylene chloride. The methylene chloride solution is treated with a small amount of decolorizing carbon, filtered and concentrated. The residue is chromatographed on 20 grams of silica gel. Elution with ethyl acetate-chloroform (1:9) gives 290 mg. of crude methyl 5-O-benzoyl-2,3-O-isopropylidine-3-methyl-β-D-ribofuranoside. Further elution with ethyl acetate-chloroform (1:9) gives about 240 mg. of mixed products. Finally, elution with ethyl acetate-chloroform (1:1) gives 420 mg. (46%) of methyl 5-O-benzoyl-3-methyl-D-ribofuranoside as an oil.

The 420 mg. (1.49 mmoles) of methyl-5-O-benzoyl-3-methyl-D-ribofuranoside from above is dissolved in 7.5 ml. of dry pyridine and cooled in an ice bath. A solution of 463 mg. (3.3 mmoles) of benzoyl chloride in 2.5 ml. of dry chloroform is added dropwise with stirring. The reaction mixture is kept at 25°C. for 24 hours and 0.5 ml. of water is added. After 30 minutes the mixture is poured onto 30 ml. of ice and water and extracted with three 30-ml. portions of chloroform. The chloroform solution is washed with cold 5% hydrochloric acid until the washings are acidic and finally with saturated sodium chloride solution. The dried ($MgSO_4$) chloroform solution is concentrated to dryness and a residue of methyl 2,5-di-O-benzoyl-3-methyl-D-ribofuranoside is obtained.

A solution of 230 mg. (0.595 mmole) of methyl 2,5-di-O-benzyl-3-methyl-D-ribofuranoside in 3 ml. of dry pyridine is treated with a solution of 90 mg. (0.64 mmole) of benzoyl chloride in 1 ml. of dry chloroform. The mixture is heated at 100°C. for 16 hours, cooled to 25°C., treated with 0.5 ml. of water and warmed to 40°C. The cooled mixture is added to ice and water and extracted with three 50-ml. portions of chloroform. The chloroform is washed with 10% hydrochloric acid until the washings are acidic and with 10% sodium bicarbonate. The dried ($MgSO_4$) chloroform layer is concentrated and the residue (370 mg.) is chromatographed on 8 grams of silica gel. Methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside (280 mg.; 95%) is obtained.

EXAMPLE 3

Preparation of 1,2-O-isopropylidene-5-O-benzoyl-3-ethyl-α-D-ribofuranose

When a Grignard reagent prepared from ethyl bromide is reacted with 1,2-O-isopropylidine-5-O-benzoyl-α-D-*erythro*-3-pentulofuranose as described for the Grignard reagent prepared from methyl iodide in Example 1, 1,2-O-isopropylidine-5-O-benzoyl-3-ethyl-α-D-ribofuranose is obtained.

EXAMPLE 4

Preparation of methyl 2,3,5-tri-O-benzoyl-3-ethyl-D-ribofuranoside

When 1,2-O-isopropylidine-5-O-benzoyl-3-ethyl-α-D-ribofuranose, obtained by the procedure of Example 3, is used in the process of Example 2 in place of 1,2-O-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose, methyl 2,3,5-tri-O-benzoyl-3-ethyl-D-ribofuranoside is obtained.

EXAMPLE 5

Preparation of 1,2-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose

A Grignard reagent, methyl magnesiumiodide, prepared from 690 mg. (28.4 mmoles) of magnesium and 3.85 grams (27.5 mmoles) of methyl iodide in 32 ml. of dry ether is added to a stirred solution of 1.0 gram (3.42 mmoles) of 1,2-O-isopropylidine-5-O-benzoyl-α-D-*erythro*-3-pentulofuranose in 100 ml. of dry ether at 5°C. After about 3 hours the reaction mixture is poured into a mixture of 50 grams of ammonium chloride, 200 ml. of ice and water, and 200 ml. of ether. The layers are separated and the aqueous phase is extracted with two 150-ml. portions of ether. The dried ($MgSO_4$) ether solution is concentrated to dryness and the residue (1.24 grams) is crystallized from ether. 524 mg. of 1,2-O-isopropylidene-5-O-benzoyl-3-methyl-α-D-ribofuranose is obtained.

EXAMPLE 6

A solution of 1.0 gram (3.25 mmols) of 1,2-O-isopropylidine-5-O-benzoyl-α-D-ribofuranose, obtained the procedure of Example 5, in 25 ml. of ethanolic hydrogen chloride is kept at 25°C for 75 minutes. The hydrogen chloride is neutralized with solid sodium bicarbonate. The mixture is filtered and the filtrate is concentrated and the residue is leached with methylene chloride. The methylene chloride solution is concentrated and the residual oil is chromatographed on silica gel. Elution with ethyl acetate-chloroform gives ethyl 5-O-benzoyl-3-methyl-D-ribofuranoside as an oil.

A solution of 1.0 gram (3.4 mmoles) of ethyl 5-O-benzoyl-3-methyl-D-ribofuranoside in 20 ml. of dry pyridine is cooled and treated with 1.0 gram (10 mmoles) of acetic anhydride. After being kept 1 hour at 25°C. the mixture is heated at 100°C. for 20 hours, cooled to 25°C., and treated with 1 ml. of water. The mixture is added to ice and water and the product is extracted with three 100-ml. portions of chloroform. The chloroform solution is washed with 10% hydrochloric acid to remove excess pyridine and finally with dilute sodium bicarbonate solution until neutral. The dried ($MgSO_4$) chloroform solution is concentrated and a residue of ethyl 2,3-di-O-acetyl-5-O-benzoyl-D-ribofuranoside is obtained.

EXAMPLE 7

Preparation of 1,2-O-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose

A Grignard reagent, methyl magnesiumiodide, prepared from 690 mg. (28.4 mmoles) of magnesium and 3.85 grams (27.5 mmoles) of methyl iodide in 32 ml. of dry ether is added to a stirred solution of 1.0 gram (3.42 mmoles) of 1,2-O-isopropylidine-5-O-benzoyl-α-D-*erythro*-3-pentulofuranose in 100 mg. of dry ether at 5°C. After about 3 hours the reaction mixture is poured into a mixture of 50 grams of ammonium chloride, 200 ml. of ice and water, and 200 ml. of ether. The layers are separated and the aqueous phase is extracted with two 150-ml. portions of ether. The dried ($MgSO_4$) ether solution is concentrated to dryness and the residue (1.24 grams) is crystallized from ether. A total of 524 mg. of 1,2-O-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose is obtained.

EXAMPLE 8

A solution of 1.0 gram (3.54 mmoles) of 1,2-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose, obtained by the procedure of Example 7, in 12 ml. of dry pyridine is cooled, stirred and treated with a solution of 750 mg. (5.3 mmoles) of benzoyl chloride in 2 ml. of dry chloroform. The mixture is kept at 25°C. for 72 hours, 0.5 ml. of water is added and the mixture is stirred for 1 hour and poured into 75 ml. of ice and water. About 25 ml. of 10% hydrochloric acid is added and the mixture is extracted with chloroform which is, in turn, washed with 10% sodium bicarbonate and saturated sodium chloride. The dried chloroform layer is concentrated and the residue when crystallized from 1 ml. of benzene and 25 ml. of petroleum ether gives 700 mg. of 1,2-O-isopropylidine-3,5-di-O-benzoyl-3-methyl-α-D-ribofuranose.

EXAMPLE 9

Preparation of 1,2-O-isopropylidene-5-O-benzoyl-3-ethyl-α-D-ribofuranose

A Grignard reagent prepared from 690 mg. (28 mmoles) of magnesium and 3.97 grams (27.5 mmoles) of ethyl bromide in 45 ml. of dry ether is added to a stirrel solution of 1.0 gram (3.42 mmoles) of 1,2-O-isopropylidine-5-O-benzoyl-α-D-*erythro*-3-pentulofuranose in 100 ml. of dry ether at 5°C. After 3 hours the

reaction is poured into a mixture of 50 grams of ammonium chloride, 200 ml. of ice and water, and 200 ml. of ether. The layers are separated and the aqueous phase is extracted with two 150-ml. portions of ether. The dried ($MgSO_4$) ether solution is concentrated to a residue of 1,2-O-isopropylidene-5-O-benzoyl-3-ethyl-α-D-ribofuranose.

EXAMPLE 10

A solution of 1.05 grams (3.54 mmoles) of 1,2-O-isopropylidine-5-O-benzoyl-3-ethyl-α-D-ribofuranose, obtained by the procedure of Example 9, in 12 ml. of dry pyridine is treated with 750 mg. (5.3 mmoles) of benzoyl chloride in 2 ml. of dry chloroform. After being kept at 25°C. for 72 hours, 0.5 ml. of water is added and the mixture is stirred for 1 hour and poured into 75 ml. of ice and water. About 25 ml. of 10% hydrochloric acid is added and the mixture is extracted with chloroform which is, in turn, washed with 10% sodium bicarbonate. The dried chloroform layer is concentrated and the 1,2-O-isopropylidine-3,5-di-O-benzoyl-3-ethyl-α-D-ribofuranose is crystallized from benzene-petroleum ether.

EXAMPLE 11

Preparation of 2,3,5-tri-O-benzoyl-3-methyl-D- ribofuranosyl bromide

A solution of 2 grams (4.04 mmoles) of methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside, as prepared in Example 2, in 10 ml. of acetic acid is cooled in an ice bath and 1 ml. of acetyl bromide is added followed by 10 ml. of a 33% solution of hydrogen bromide in acetic acid. After 15 minutes at 0—5°C., the solution is kept at 25°C. for 35 minutes. Concentration of the solution gives a residual oil which is freed of last traces of hydrogen bromide by distilling 3 portions of dry toluene and 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide is obtained.

EXAMPLE 12

Preparation of 2,3-di-O-acetyl-5-O-benzoyl-3-methyl-D-ribofuranosyl bromide

A solution of 1.52 grams (4.0 mmoles) of ethyl 2,3-di-O-acetyl-5-O-benzoyl-3-methyl-D-ribofuranoside, as prepared in Example 6, in 10 ml. of acetic acid is cooled in an ice bath and 1 ml. of acetyl bromide is added followed by 10 ml. of a 33% solution of hydrogen bromide in acetic acid. After being kept at 25°C. for 50 minutes, the solution is concentrated to a residue of 2,3-di-O-acetyl-5-O-benzoyl-3-methyl-D-ribofuranosyl bromide. Last traces of hydrogen bromide and acetic acid are removed by distilling 3 portions of dry toluene from the product.

EXAMPLE 13

Preparation of 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl chloride

A solution of 2 grams (4.0 mmoles) of methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside, as prepared in Example 2, in 10 ml. of acetic acid is cooled in an ice bath and 1 ml. of acetyl chloride is added followed by 10 ml. of a 20% (w/w) solution of hydrogen chloride in acetic acid. After 48 hours at 25°C. the solution is concentrated. Three portions of dry toluene are distilled from the residue to remove last traces of acetic acid and hydrogen chloride and a residue of 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl chloride is obtained.

EXAMPLE 14

Preparation of 3-methyl-D-ribofuranose

A solution of 2.0 grams (4.0 mmoles) of methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside, as prepared in Example 2, in 50 ml. of methanol is treated with 5 ml. of 0.5 *N* barium methoxide in methanol. After being refluxed for 30 minutes, the solution is concentrated to about 10 ml. and diluted with 50 ml. of water. After adding 5 ml. of 0.5 *N* sulfuric acid, the precipitated barium sulfate is filtered. The filtrate is acidified (pH2) with hydrochloric acid and kept at 60°C. for several hours. Concentration of the aqueous solution gives a residue containing 3-methyl-D-ribofuranose.

EXAMPLE 15

Preparation of 1,2-di-O-acetyl-3,5-di-O-benzoyl-3-methyl-ribofuranose

To a mixture of 130 ml. of acetic acid and 14.4 ml. of acetic anhydride is added 11.5 grams (28 mmoles) of 3,5-di-O-benzoyl-1,2-O-isopropylidine-3-methyl-α-D-ribofuranose, as prepared in Example 8. During a 45-minute period 7.8 ml. of concentrated sulfuric acid is added dropwise to the stirred mixture. An ice bath is used to maintain the temperature of the reaction mixture at 15—20°C. during the addition

of the sulfuric acid. After being kept at room temperature 16 hours, the solution is poured into 630 ml. of ice water. The product is extracted with two 120-ml. portions of chloroform which is in turn washed with three 75-ml. portions of 1 *N* sodium bicarbonate. Concentration of the dried ($MgSO_4$) chloroform solution gives a residue of 1,2-di-O-acetyl-3,5-di-O-benzoyl-3-methyl-D-ribofuranose.

EXAMPLE 16

Preparation of 1,2-di-O-propionyl-3,5-di-O-benzoyl-3-methyl-D-ribofuranose

To a mixture of 150 ml. of propionic acid and 17 ml. of propionic anhydride is added 11.5 grams (28 mmoles) of 3,5-di-O-benzoyl-1,2-O-isopropylidine-3-methyl-α-D-ribofuranoside, as prepared in Example 8. During a 45-minute period 7.8 ml. of concentrated sulfuric acid is added dropwise to the stirred mixture. An ice bath is used to maintain the temperature of the reaction mixture at 15—20°C. during the addition of the sulfuric acid. After being kept at room temperature 16 hours, the solution is poured into 630 ml. of ice water. The product is extracted with two 120-ml. portions of chloroform which is, in turn, washed with three 75-ml. portions of 1 N sodium bicarbonate. Concentration of the dried ($MgSO_4$) chloroform solution gives a residue of 1,2-di-O-propionyl-3,5-di-O-benzoyl-3-methyl-D-ribofuranose.

EXAMPLE 17

Preparation of 1,2-di-O-butyryl-3,5-di-O-benzoyl-3-methyl-D-ribofuranose

To a mixture of 160 ml. of butyric acid and 196 ml. of butyric anhydride is added 11.5 grams (28 mmoles) of 3,5-di-O-benzoyl-1,2-O-isopropylidine-3-methyl-α-D-ribofuranoside, as prepared in Example 8. During a 45-minute period 7.8 ml. of concentrated sulfuric acid is added dropwise to the stirred mixture. An ice bath is used to maintain the temperature of the reaction mixture at 15—20°C. during the addition of the sulfuric acid. After being kept at room temperature 16 hours, the solution is poured into 630 ml. of ice water. The product is extracted with two 120-ml. portions of chloroform which is, in turn, washed with three 75-ml. portions of 1 *N* sodium bicarbonate. Concentration of the dried ($MgSO_4$) chloroform solution gives a residue of 1,2-di-O-butyryl-3,5-di-O-benzoyl-3-methyl-D-ribofuranose.

EXAMPLE 18

Preparation of 2,3,5-tri-O-benzoyl-3-ethyl-D-ribofuranosyl bromide

A solution of 2.0 grams (4.0 mmoles) of methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside, as prepared in Example 2, in 10 ml. of acetic acid is cooled in an ice bath and 1 ml. of acetyl bromide is added followed by 10 ml. of a 33% solution of hydrogen bromide in acetic acid. After 15 minutes at 0—5°C. the solution is kept at 25°C. for 35 minutes. Concentration of the solution gives a residual oil which is freed of last traces of hydrogen bromide and acetic acid by distilling 3 portions of toluene and 2,3,5-tri-O-benzoyl-3-ethyl-D-ribofuranosyl bromide is obtained.

EXAMPLE 19

Preparation of 3-ethyl-D-ribofuranose

A solution of 2.05 grams (4.0 mmoles) of methyl 2,3,5-tri-O-benzoyl-3-ethyl-D-ribofuranoside, as prepared in Example 4, in 50 ml. of methanol is treated with 5 ml. of 0.5 *N* barium methoxide in methanol. After being refluxed for 30 minutes, the solution is concentrated to about 10 ml. and diluted with 50 ml. of water. After adding 5 ml. of 0.5 N sulfuric acid, the precipitated barium sulfate is filtered. The filtrate is acidified (pH 2) with hydrochloric acid and kept at 60°C. for several hours. Concentration of the aqueous solution gives a residue containing 3-ethyl-D-ribofuranose.

EXAMPLE 20

Preparation of 1,2-di-O-acetyl-3,5-di-O-benzoyl-3-ethyl-O-ribofuranose

To a mixture of 13.0 ml. of acetic acid and 14.4 ml. of acetic anhydride is added 11.8 grams (28 mmoles) of 1,2-O-isopropylidine-3,5-di-O-benzoyl-3-ethyl-α-D-ribofuranose, as prepared in Example 10. During a 45-minute period 7.8 ml. of concentrated sulfuric acid is added dropwise to the stirred mixture. An ice bath is used to maintain the temperature of the reaction mixture at 15—20°C. during the addition of the sulfuric acid. After being kept at room temperature for 16 hours, the solution is poured into 630 ml. of ice water. The product is extracted with two 120-ml. portions of chloroform which is, in turn, washed with three 75-ml. portions

of 1 *N* sodium bicarbonate. Concentration of the dried ($MgSO_4$) chloroform solution gives a residue of 1,2-di-O-acetyl-3,5-di-O-benzoyl-3-ethyl-D-ribofuranose.

The following two examples, 21 and 22, are illustrative of the value of the compounds of the present invention as starting materials for the preparation of important nucleosides. The nucleoside products are claimed in our copending application No. 49924/66 (Serial No. 1,163,103). It is evident that other nucleoside compositions may be prepared by selecting other compounds of this invention as starting materials.

EXAMPLE 21

Preparation of 9-(3-methyl-D-ribofuranosyl)-6-chloropurine

About 100 ml. of xylene is distilled from a suspension of 6.55 grams (16.8 mmoles) of chloromercuri-6-chloropurine in 460 ml. of xylene in order to remove the last traces of water. A solution of 8.25 grams (16.8 mmoles) of 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide in 40 ml. of dry xylene is added to the stirred suspension at 25°C. The mixture is refluxed for 2 hours. The hot mixture is filtered to remove insoluble material. The filtrate is concentrated to 150 ml. and diluted with 300 ml. of petroleum ether. The mixture is kept at 5°C. for one hour and filtered. The solid is washed with three 20-ml. portions of petroleum ether and dried. The crude product is dissolved in 300 ml. of hot chloroform and washed with two 80-ml. portions of 30% potassium iodide solution and two 80-ml. portions of water. The dried ($MgSO_4$) chloroform layer is concentrated, and 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine is obtained. The product is purified by chromatography on a short alumina column in chloroform.

A solution of 479 mg. (1.0 mmole) of 9-(2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl)-6-chloropurine, in 20 ml. of cold methanol containing 2 grams of anhydrous ammonia is kept at 5°C. for 20 hours. The solution is concentrated at reduced pressure and at a temperature of less than 20°C. The residue is recrystallized from methanol to give 9-(3-methyl-D-ribofuranosyl)-6-chloropurine.

EXAMPLE 22

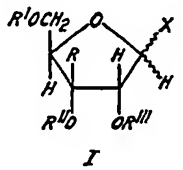
Preparation of 3'-methyladenosine

A boiling mixture of 605 mg. (2 mmoles) of 9-(3-methyl-D-ribofuranosyl)-6-chloropurine, in 30 ml. of anhydrous methanol is treated with a solution prepared by saturating 20 ml. of 0.1 N sodium methoxide in methanol with methyl mercaptan. After being refluxed for about 30 minutes the solution is cooled and concentrated to dryness. The residue is dissolved in hot water and on cooling, 9-(3-methyl-D-ribofuranosyl)-6-methylthiopurine separates.

A mixture of 1.26 grams (1.8 mmoles) of 9-(2,3,5-tri-O-benzoyl-3-methyl-β-D-ribofuranosyl)-6-benzamidopurine and 13 ml. of dry methanol is treated with a solution of sodium methoxide prepared from 70 mg. (3 mmoles) of sodium and 3 ml. of methanol. After the mixture is refluxed for 2 hours, it is concentrated and the residue is dissolved in 50 ml. of water. The pH is adjusted from 11.5 to 5.2 with a few drops of acetic acid. The solution is extracted with five 20-ml. portions of chloroform and the water layer is filtered and concentrated to dryness. The residue is dissolved in methanol and 430 mg. of impure amorphous product is precipitated with ether. The filtrate is concentrated to dryness and the residue is crystallized from a water solution. Recrystallization from 0.7 ml. of water gives 126 mg. of 3'-methyladenosine.

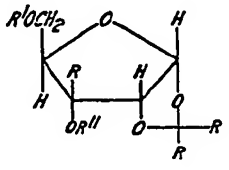
WHAT WE CLAIM IS:—

1. A compound of the formula:



I

or



III

where R is a C_{1-4} alkyl radical, X is a halogen atom or a hydroxy, C_{1-4} alkoxy, alkanoyloxy, aroyloxy, alkoxyaroyloxy, haloaroyloxy or nitrobenzoyloxy radical and each of R′, R″ and R‴ is a hydrogen atom, or an alkanoyl, aroyl, alkoxyaroyl, haloaroyl or nitrobenzoyl radical provided that, in Formula I, when X is an alkanoyloxy, aroyloxy, alkoxyaroyloxy, haloaroyloxy or nitrobenzoyloxy radical R′, R″ and R‴ are not hydrogen atoms.

2. A compound as claimed in claim 1, in which R is a methyl radical.

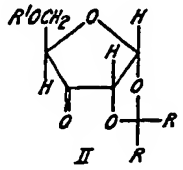
3. A compound as claimed in claim 1, in which R is an ethyl radical.

4. 1,2-O-Isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose.

5. 2,3,5-Tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide.

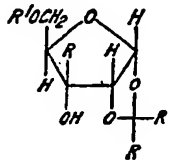
6. 1,2-Di-O-acetyl-3,5-di-O-benzoyl-3-ethyl-D-ribofuranose.

7. The process that comprises treating a compound of the formula:



II

where R and R′ are as defined in claim 1, with a Grignard reagent of the formula RMgX′, where R is as defined in claim 1 and X′ is a halogen atom to produce a compound of the formula:



IIIa

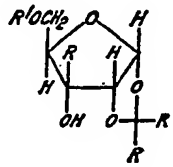
where R and R′ are as defined in claim 1.

8. A process as claimed in claim 7, carried out at a temperature of from 5°C to 80°C for a period of from a few minutes to five hours.

9. A process as claimed in claim 7 or 8, in which the Grignard reagent is methyl magnesiumbromide, ethyl magnesiumbromide, methyl magnesiumchloride, ethyl magnesiumchloride, methyl magnesiumiodide, ethyl magnesiumiodide or propylmagnesium bromide.

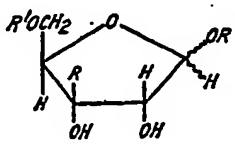
10. The process that comprises treating 5-O-benzoyl-1,2-O-isopropylidine-D-*erythro*-3-pentulofuranose with methyl magnesium iodide at 5°C for 3 hours to form 1,2-O-isopropylidine-5-O-benzoyl-3-methyl-α-D-ribofuranose.

11. The process that comprises subjecting a compound of formula:



IIIa

where R and R′ are as defined in claim 1 to acidic alcoholysis to produce a compound of general formula:



where R and R′ are as defined in claim 1.

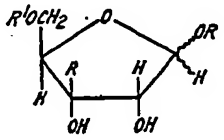
12. A process as claimed in claim 11, carried out at a temperature of 5°C to 60°C for a period of from a few minutes to five hours.

13. A process as claimed in Claim 11 or 12, including the step of preparing the starting material by a process as claimed in claim 7, 8 or 9.

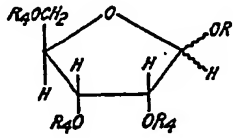
14. The process that comprises treating 1,2-O-isopropylidene-5-O-benzoyl-3-methyl-α-D-ribofuranose with methanolic hydrogen chloride at 25°C for 75 minutes to produce methyl 5-O-benzoyl-3-methyl-D-ribofuranoside.

15. A process as claimed in claim 14, including the step of preparing the starting material by a process as claimed in claim 10.

16. The process that comprises subjecting a compound of formula:



where R and R′ are as defined in claim 1 to basic acylation to produce a compound of general formula:



where R is a C_{1-4} alkyl radical and each R_4 is an alkanoyl, aroyl, alkoxyaroyl, haloaroyl or nitrobenzoyl radical.

17. A process as claimed in claim 16, carried out at a temperature of 20°C to 100°C for a period of from 2 to 72 hours.

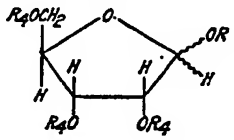
18. A process as claimed in claim 16 or 17, using benzoyl chloride, benzoyl bromide, nitrobenzoyl chloride, acetic anhydride or propionic anhydride as an acylating agent.

19. A process as claimed in claim 16, 17 or 18, including the step of preparing the starting material by a process as claimed in claim 11, 12 or 13.

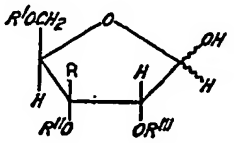
20. The process that comprises acylating methyl 5-O-benzoyl-3-methyl-D-ribofuranoside with benzoyl chloride in the presence of pyridine at 100°C for 16 hours to give methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside.

21. A process as claimed in claim 20, including the step of preparing the starting material by a process as claimed in claim 14 or 15.

22. The process that comprises subjecting a compound of formula:



where R is a C_{1-4} alkyl radical and each R_4 is an alkanoyl, aroyl, alkoxyaroyl, haloaroyl or nitrobenzoyl radical to basic solvolysis, followed by acid hydrolysis, to produce a compound of general formula:

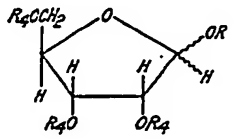


in which R, R′, R″ and R‴ are as defined in claim 1.

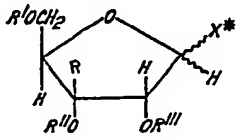
23. A process as claimed in claim 22, in which the basic solvolysis is carried

out using a C_{1-4} alcohol at a temperature of 15°C to 60°C and the acid hydrolysis carried out with hydrochloric, hydrobromic or sulfuric acid at a temperature of 5°C to 50°C for from 2 to 24 hours.

24. The process that comprises subjecting a compound of formula:



where R is a C_{1-4} alkyl radical and each R_4 is an alkanoyl, aroyl, alkoxyaroyl, haloaroyl or nitrobenzoyl radical to a halogen replacement reaction to produce a compound of general formula:



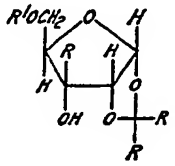
in which R, R′, R″ and R‴ are as defined in claim 1 and X* is a halogen atom.

25. A process as claimed in claim 24, carried out at a temperature of 0°C to 30°C using a hydrogen halide HX* in a solvent.

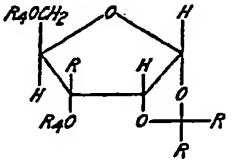
26. The process that comprises reacting methyl 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranoside with hydrogen bromide in acetic acid at 0°C to 5°C for 15 minutes and then at 25°C for 35 minutes to produce 2,3,5-tri-O-benzoyl-3-methyl-D-ribofuranosyl bromide.

27. The process as claimed in any one of claims 22—26, including the step of preparing the starting material by a process as claimed in any one of claims 16—21.

28. The process that comprises subjecting a compound of formula:



where R and R′ are as defined in claim 1 to acylation under basic conditions to produce a compound of general formula:

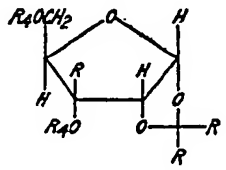


in which R and R_4 are as defined in claim 16.

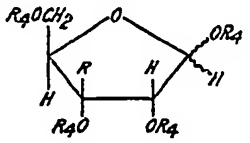
29. A process as claimed in claim 28, using benzoyl chloride, benzoyl bromide, nitrobenzoyl chloride, acetic anhydride or propionic anhydride as an acylating agent and pyridine, dimethylaniline, N-methylmorpholine or sodium acetate in an inert solvent to provide the basic conditions.

30. A process as claimed in claim 28 or 29, including the step of preparing the starting material by a process as claimed in claim 7, 8 or 9.

31. The process that comprises subjecting a compound of formula:



in which R and R_4 are as defined in claim 16 to hydrolysis with a strong acid, followed by acylation under acidic conditions, to produce a compound of general formula:



in which R_4 is as defined in claim 16.

32. A process as claimed in claim 31, in which the hydrolysis and acylation are carried out at 5°C to 50°C for from two to 24 hours.

33. A process as claimed in claim 31 or 32, including the step of preparing the starting material by a process as claimed in any one of claims 28—30.

34. A process substantially as hereinbefore described in any one of Examples 1—20 that results in the production of a compound as claimed in claim 1.

35. A compound as claimed in claim 1, when prepared by a process as claimed in any one of claims 7—34 or its obvious chemical equivalent.

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